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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/001,737	12/31/1997	LEE MIZZEN	870109.408	7028

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 04/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/001,737	MIZZEN ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8,19-24,31-35 and 38-45* is/are pending in the application.

4a) Of the above claim(s) *4,8,32 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,6,19-24,31,38,39 and 41-45* is/are rejected.

7)☒ Claim(s) *3, 5, 7, 33, 35 and 40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Seqence reports (3 pages)*.

Prosecution Reopened

1) In view of the Appeal Brief filed on 01/26/05, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below. To avoid abandonment of the application, Appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

Appeal Brief

2) Acknowledgment is made of Applicants' Appeal Brief filed 01/26/05 in response to the final Office Action mailed 06/09/04.

Status of Claims

3) Claims 1, 9-18, 25-30, 36 and 37 have been canceled.

Claims 2-8, 19-24, 31-35 and 38-45 are pending.

Claims 4, 8, 32 and 34 are withdrawn from consideration as being directed to non-elected invention.

Claims 2, 3, 5-7, 19-24, 31, 33, 35 and 38-45 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been

previously cited and made of record.

Objection(s) Maintained

6) The objection to claims 3, 5-7, 20, 33, 35, 38 and 39 maintained in paragraph 10 of the Office Action mailed 06/09/04 is still maintained for reasons set forth therein.

7) The objection to claims 19, 21-24, 31, 33, 35 and 40 made in paragraph 26 of the Office Action mailed 06/09/04 is still maintained for reasons set forth therein.

Rejection(s) Withdrawn

8) The rejection of claim 5 made in paragraph 12 of the Office Action mailed 06/06/03 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is withdrawn in light of Applicants' argument. Applicants have gone on the record stating that the complementary sequence claimed in claim 5 is complementary to at least 25% of contiguous nucleotide bases (i.e., at least 409 contiguous nucleotides) from 15-1652 of SEQ ID NO: 7 and **must** extend from the first specified nucleotide to the last.

9) The rejection of claim 2 made in paragraph 15 of the Office Action mailed 06/06/03 and maintained in paragraph 21 of the Office Action mailed 06/09/04 under 35 U.S.C § 102(b) as being anticipated by Hamel *et al.* (WO 96/40928, already of record), is withdrawn upon further consideration. A new rejection is set forth below.

10) The rejection of claim 7 made in paragraph 22(a) of the Office Action mailed 06/09/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' arguments. Applicants go on the record stating that the phrase 'is selectively bound by an antibody' is a functional limitation of the polypeptide that is encoded by the nucleic acid molecule.

11) The rejection of claims 19-24, 31 and 41made in paragraphs 22(c) and 22(b) of the Office Action mailed 06/09/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn.

12) The rejection of claims 3, 5, 19-24, 31 and 40 made in paragraph 21 of the Office Action mailed 06/09/04 under 35 U.S.C § 102(e) as being anticipated by Kunsch *et al.* (US 6,420,135, filed 10/31/1996), is withdrawn in light of Applicants' arguments. Applicants have gone on the record stating that: (a) the complementary sequence claimed in claim 5 is complementary to at least 25% of contiguous nucleotide bases (i.e., at least 409 contiguous nucleotides) from 15-1652 of SEQ ID NO: 7 and **must** extend from the first specified nucleotide to the last; and (b) complementary nucleic acid

molecules of claims 3 and 40 **must** include a sequence that is complementary to the *entire recited portion of SEQ ID NO: 7*, which is 1638 nucleotides long. Thus, the instant invention specifically excludes partial complements from the scope of the claims.

13) The rejection of claims 3 and 40 made in paragraph 24 of the Office Action mailed 06/09/04 under 35 U.S.C § 102(b) as being anticipated by Podbielski (1995) is withdrawn in light of Applicants' argument. Applicants have gone on the record stating that the complementary nucleic acid molecule of claims 3 and 40 **must** include a sequence that is complementary to the *entire* recited portion, from nucleotides 15-1652 of SEQ ID NO: 7, which is 1638 nucleotides long. Thus, Applicants have specifically excluded partial complements from the scope of the claims.

Rejection(s) Maintained

14) The rejection of claims 6, 19-24, 31, 38 and 39 made in paragraph 12 of the Office Action mailed 06/06/03 under 35 U.S.C § 112, first paragraph, as containing inadequate written description, is maintained for reasons set forth therein and herebelow.

Applicants contend that the *Written Description Guidelines* (*Federal Register*, vol. 66, no. 4, Notices pp. 1099-1111, 05 January 2001) do not have the force and effect of law. Appellants cite *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991) and state that an adequate description is one that describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor has possession of the claimed invention. Applicants argue that possession may be shown in a variety of ways, for example, by presenting drawings of the claimed invention, or structural chemical formulas. Applicants cite *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55 (1998) and *Amgen, Inc. v. Chugai Pharmaceutial,* 927 F.2d 1200 (Fed. Cir. 1991) and state that Applicant may also describe distinguishing identifying characteristics. Applicants submit that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice; reduction to drawings; or disclosure of relevant identifying characteristics. Applicants point to MPEP 2163(3)(a)(ii) that cites *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997); *Enzo Biochem.*, 323 F.3d at 966, 63 USPQ2d at 1615 and *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and state that a 'representative number of species' means that the species that are adequately described are representative of the entire genus. Appellants point to MPEP 2163(II)(A) that cites *Wertheim*, 541 F.2d 257 (CCPA 1976) and state

that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed.

With regard to the Office's noting of the lack of teaching in the specification as to the distinguishing attributes that are shared by the members of the genus, Applicants state that: (a) they have made clear what attributes the claimed nucleic acid molecules have in common; and (b) one of ordinary skill in the art would surely recognize those attributes. Applicants submit that it is clear from the plain language of the claims that all of the nucleic acid molecules must include a certain sequence. Applicants state that the nucleic acid molecules of claim 5 must all include a sequence that is identical to at least 25% of the contiguous nucleotides of SEQ ID NO: 7 from nucleotides 15-1652, and that such sequences are explicitly described in the specification at page 5, line 28 through page 6, line 3. With this, Applicants assert that they have described in their specification a specific sequence that is represented by nucleotides 15-1652 of SEQ ID NO: 7 and 'variants' thereof that contain at least 25% of the contiguous nucleotides of SEQ ID NO: 7 from nucleotide 15 to nucleotide 1652. Applicants opine that a simple mathematical exercise is required to determine how many nucleotides constitute at least 25% of the reference sequence. Applicants further submit the following arguments:

- By describing SEQ ID NO: 7 and by specifying a particular portion defined by the 'at least 25%' of SEQ ID NO: 7, Applicants have described the necessary common attributes of all of the nucleic acid molecules claimed, i.e., molecules having sequences in addition to those of SEQ ID NO: 7 and 'homologues' of SEQ ID NO: 7. Writing out one exemplary sequence after another would add nothing more. Given Applicants' description, one of ordinary skill in the art would have no difficulty in perceiving the sequences described and in concluding that Applicants were in possession of those sequences.

- With regard to the Office's position that one of skill in the art cannot envision the detailed chemical structure of the encompassed nucleic acid molecule species absent precise description, Applicants cite *Fiers v. Ravel*, 984 F.2d 1164, 1189 (Fed. Cir. 1993) and state that while one does not need to have carried out one's invention before filing a patent application, one does need to describe that invention with particularity. Applicants contend that they have described the nucleic acid molecules they now claim with particularity in such a way that one of ordinary skill in the art could conclude that Applicants possessed those molecules.

- With regard to the lack of structure-function correlation raised by the Office for the genus of nucleic acid molecule variants, complements or homologues (other than the one consisting of SEQ ID NO: 7 and the one consisting of nucleotides 15-1652 from SEQ ID NO: 7), Applicants cite parts of the Office Action and parts of the *Written Description Guidelines*, and submit that the Office should look for an established correlation between structure and function when Applicants provide an incomplete structure. Applicants argue that they have more than 'minimal structure', i. e., the complete sequence of SEQ ID NO: 7, and have described particular and readily identifiable 'variants' that constitute the claimed invention. Applicants cite *Fiers v. Ravel*, 984 F.2d 1164, 1189 (Fed. Cir. 1993) and state that the Office's continued reliance of *Fiers* is not understood. Applicants refer to Ravel within *Fiers* and state that the lack of adequate description there was because Ravel did not provide the sequence of the DNA he attempted to claim. With this, Applicants conclude that the facts of *Fiers*, with respect to Ravel, are contrary to the facts of the instant case, where Applicants do disclose the sequence of the DNA they wish to claim. Applicants further discuss the Federal Circuit's consideration, at 1172 in *Fiers*, of a specification belonging to Sugano that 'Sugano's application satisfies the written description requirement since it sets forth the complete and correct nucleotide sequence of a DNA coding for β-IF' and conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Sugano was in possession of the DNA coding for β-IF.

- With regard to the Office's citation of *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991), Applicants state that claim 2 in *Amgen* covered a purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin, but there the actual sequence was not described in the specification. Applicants conclude that both *Fiers* and *Amgen* stand for the proposition that, absent structural information, the claiming of a gene by mere function --where there is 'simply a wish' to know its identity-- does not satisfy the written description requirement, and that actual reduction to practice is required when conception is otherwise incomplete. Applicants conclude that the instant facts are significantly different in that Applicants' specification does not merely recite the name of a gene or a desired function, but instead describes the specific nucleic acid sequences encompassed by the claims. Applicants are of opinion that they have reduced their invention to practice and provided a thoroughly adequate written description.

- With regard to claims 6, 38 and 39, which cover isolated nucleic acid molecules that include a sequence encoding a polypeptide that is at least 95%, 97% or 98% homologous, respectively, to SEQ ID NO: 8, Applicants submit that: (a) the sequence of the polypeptide designated SEQ ID NO: 8; (b) the specification at page 6, lines 5 and 6 provides a clear statement that 'a variant of Hsp60 that is at least 95% homologous to a polypeptide ... of SEQ ID NO: 8'; (c) the specification at the paragraph bridging pages 11 and 12 describe that the homology may also be greater than 97% or 98%; (d) by specifying that a variant sequence must remain at least 95%, 97% or 98% homologous to the reference sequence of SEQ ID NO: 8, Applicants have described the necessary common attributes of all of the nucleic acid molecules claimed in claim 6; and (e) there was no need to exemplify sequence after sequence. Applicants further submit the following argument:

> By reference to a minimum homology, Appellants adequately described not only a representative number of species, but the entire genus of nucleic acids, as one of ordinary skill could immediately vary the sequence *in any given way* and determine whether the requisite level of homology was retained.

With regard to the rejected dependent claims 19-24 and 31, Applicants state that the compositions covered by these claims are described in the specification at page 7, lines 18-29; page 11, lines 5-15; and page 15, line 28 through page 23, line 5. Applicants contend that the various sequences, vectors and cells are described on pages 37-39 and that the Office has made no specific comments regarding the adequacy of disclosure of these compositions.

- With regard to the Office's comments on the open claim language of the claims, Applicants state that the claims cover 'portions' of SEQ ID NO: 7 and 'homologues' of SEQ ID NO: 7 and nucleic acid molecules that include at least one additional nucleotide at either end of those defined portions or homologues. Applicants submit that all of these nucleic acids must still have the common attributes Applicants so fully described when they described the sequence by virtue of its minimal content, i.e., 'at least 25% of ...' or 'at least 95% homologous to ...'. Applicants conclude that the open claim language does broaden the scope of the claims, but does not broaden it beyond the scope of Applicants' description.

Applicants' arguments have been carefully considered, but are not persuasive for the various reasons set forth herebelow:

Via the drawings of the claimed invention, or structural chemical formulas, Applicants have shown that they had possession of an isolated nucleic acid molecule consisting of SEQ ID

NO: 7 and a nucleic acid molecule consisting of nucleotides 15-1652 of SEQ ID NO: 7. However, Applicants did not have possession of variant and homologue nucleic acid molecules of SEQ ID NO: 7 encoding polypeptide variants comprising amino acid sequences that are at least 95%, 97% or 98% homologous to the amino acid sequence of SEQ ID NO: 8, as claimed.

Contrary to Applicants' assertion, the facts of *Fiers*, with respect to Ravel, are applicable in the instant case, because Applicants have not disclosed the sequence of the nucleic acid molecules they are now claiming, i.e., variant nucleic acid molecules encoding polypeptide variants having 95%, 97% or 98% homologous to SEQ ID NO: 8 they wish to claim. Contrary to the situation in *Sugano* discussed in *Fiers*, instant specification does not satisfy the written description requirement since it does not set forth the complete nucleotide sequence of a nucleic acid molecule coding for a polypeptide comprising an amino acid sequence that is at least 95%, 97% or 98% homologous to SEQ ID NO: 8, and therefore does not convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the nucleic acid molecule coding for a polypeptide comprising an amino acid sequence that is at least 95%, 97% or 98% homologous to SEQ ID NO: 8. Similar to the situation in *Amgen*, the precise structural information on nucleic acid molecules coding for polypeptides comprising amino acid sequences that are at least 95%, 97% or 98% homologous to SEQ ID NO: 8 is absent in the instant specification. In addition, there is also, absence of a function. Thus, what is left is indeed 'simply a wish' which does not satisfy the written description requirement. Applicants are correct that actual reduction to practice is required when conception is otherwise incomplete, which in the instant case is lacking.

The scope of the claims includes numerous structural variants internal to SEQ ID NO: 7 and in the sequence outside of SEQ ID NO: 7 within the nucleic acid molecule that 'comprises' SEQ ID NO: 7. The genus is highly variant, and a significant number of structural differences between genus members are included or permitted. Because the genus is highly variable and since the disclosure and claims fail to describe the common attributes or characteristics that identify members of the genus, a nucleic acid molecule 'consisting' of SEQ ID NO: 7 is insufficient to describe the genus of nucleic acid molecules 'comprising' SEQ ID NO: 7 and variants thereof encoding polypeptide variants comprising amino acid sequences a least 95%, 97% and 98% homologous to SEQ ID NO: 8. Applicants have not described a function which is shared by a nucleic acid molecule 'consisting' of SEQ ID NO: 7 encoding a polypeptide 'consisting' of the

amino acid sequence of SEQ ID NO: 8 and by nucleic acid molecule variant species 'comprising' nucleic acid sequences encoding polypeptide variants 'comprising' amino acid sequences that are at least 95%, 97% or 98% homologous to SEQ ID NO: 8. Therefore, one of skill in the art would reasonably conclude that the instant disclosure fails to provide for a representative number of species to describe the genus. The single described species of a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO: 7 that encodes the polypeptide consisting of the amino acid sequence of SEQ ID NO: 8 is not representative of the entire genus that includes variants or homologues. Clearly, Applicants were not in possession of the claimed genus. The description of SEQ ID NO: 7 and specifying of a particular portion defined by the 'at least 25%' of SEQ ID NO: 7 are insufficient to describe the necessary common attributes of all of the nucleic acid molecules claimed, i.e., 'variants' or 'homologues' of SEQ ID NO: 7 encoding polypeptide variants 'comprising' amino acid sequences that are at least 95%, 97% or 98% homologous to SEQ ID NO: 8. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 makes clear that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*'. See *Vas-Cath* at page 1117. The specification does not 'clearly allow persons of ordinary skill in the art to recognize that [she or he] invented what is claimed'. See *Vas-Cath* at page 1116. The rejection stands.

15) The rejection of claims 41-45 made in paragraph 21 of the Office Action mailed 06/09/04 under 35 U.S.C § 102(e) as being anticipated by Kunsch *et al.* (US 6,420,135, filed 10/31/1996, already of record), is maintained for reasons set forth therein and herebelow.

It is noted that Applicants have not advanced any arguments with regard to Kunsch's disclosure of the nucleic acid fragments claimed in the instant claims 41-45. However, Applicants acknowledge Kunsch's anticipatory teaching of 18 contiguous nucleotides that are complementary to SEQ ID NO: 7 (see paragraph bridging pages 13 and 14 of Applicants' Appeal Brief filed 01/26/05).

Kunsch *et al.* taught an isolated nucleic acid molecule consisting of 6 or more nucleotides of SEQ ID NO: 1-391 and complementary sequences thereto operably associated with a regulatory sequence that controls gene expression (see abstract; claims; third paragraph in column 9; fourth paragraph in column 4; last paragraph in column 3; and sixth paragraph in column 25). One such nucleic acid molecule is SEQ ID NO: 77 (see the sequence alignment report attached to the Office

Action mailed 06/09/04). Diagnostic fragments (DF) of nucleic acid molecules with 17 contiguous nucleotide bases that selectively hybridize to *S. pneumoniae* sequences; expression vectors comprising the nucleic acid fragments; and host cells comprising such nucleic acid molecules are taught (see fifth paragraph in column 13; first paragraph in column 14; third and fourth paragraphs in column 15; and paragraph bridging columns 16 and 17). Diagnostic primers and probes with 18 nucleotide bases that recognize the *S. pneumoniae* nucleotide sequences under high stringency conditions, such as, 65°C in 6 x SSC, and kits containing such primers or probes and reagents such as PBS (i.e., pharmaceutically acceptable carrier or diluent) or Tris-buffers are taught (see third and fourth paragraphs in column 19; second paragraph in column 14; second full paragraph in column 35; and column 24). The sequence alignment report already provided to Applicants show stretches of contiguous nucleotide bases in the prior art nucleotide sequence that consist of 12 (CGTCAAATTGCT) and 17 (TTGAACAAGATTCGTGG, or TTTGACCGTGGTTACCT) bases that are 100% structurally identical with fragments of the instantly recited SEQ ID NO: 7 from *S. pyogenes*. Kunsch thus taught that both *S. pneumoniae* and *S. pyogenes Hsp* polynucleotide fragments consisting of 12, 17 and 18 nucleotide bases are identical in structure. The rejection stands.

Rejection under 35 U.S.C § 112, First Paragraph (New Matter)

16) Claims 38 and 39 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 38 and 39 include the limitations: comprises an amino acid sequence 'that is at least 97% homologous to ... SEQ ID NO: 8' and comprises an amino acid sequence 'that is at least 98% homologous to ... SEQ ID NO: 8' respectively. While the specification provides descriptive support for *S. pyogenes* Hsp60 genes encoding polypeptides having 'greater than 97% or 98% homology', the specification does not appear to be supportive of *S. pyogenes* Hsp60 genes encoding polypeptides having 'at least 97% or 98% homology' to SEQ ID NO: 8 as recited in the instant claims. The term 'greater than' is not the same as the term 'at least' in terms of scope. Therefore, the above-identified new limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but

also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitations, or to remove the new matter from the claims.

Rejection under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

17) Claims 6, 38 and 39 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 8, does not reasonably provide enablement for an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid that is 'at least 95%', 'at least 97%', or 'at least 98%' homologous to SEQ ID NO: 8, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims are drawn to an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid that is 'at least 95%', 'at least 97%', or 'at least 98%' homologous to SEQ ID NO: 8. A review of the instant specification indicates that the polypeptide comprising the amino acid sequence of SEQ ID NO: 8 is described in the specification as a heat shock protein of *S. pyogenes* and its structure disclosed. The isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 7 which encodes the polypeptide of SEQ ID NO: 8 is disclosed. However, the precise structure of the nucleic acid molecule encoding a polypeptide comprising an amino acid sequence that is 'at least 95%', 'at least

97%', or 'at least 98%' homologous to SEQ ID NO: 8 (i.e., a polypeptide variant) is not disclosed, without which one of skill in the art cannot make and use the instantly claimed product, without undue experimentation. The specification intends therapeutic, immunoprophylactic and diagnostic utility for the above-cited polypeptide variants of SEQ ID NO: 8. This requires that the polypeptide variants with at least 2-5% sequence dissimilarity with SEQ ID NO: 8 that are encoded by the claimed nucleic acid molecules retain their therapeutic, immunoprophylactic and diagnostic properties in order to accomplish the intended objectives of the invention. In other words, the encoded polypeptide variant having at least 5%, 3% or 2% sequence dissimilarity with the amino acid sequence of SEQ ID NO: 8 is *required* to confer therapeutic and immunoprophylactic effects and retain *S. pyogenes*-specific diagnostic potential. However, the instant specification does not teach how to produce a variant nucleic acid molecule that encodes a polypeptide of the amino acid sequence SEQ ID NO: 8 with at least 5%, 3% or 2% of its amino acids varied or modified in such a way that the resultant polypeptide variant still maintains its therapeutic and immunoprophylactic effects and *S. pyogenes*-specificity for diagnostic purposes. In other words, neither the specification nor the art discloses a nucleic acid molecule that encodes a polypeptide variant that is at least 5%, 3% or 2% non-identical to the amino acid sequence of SEQ ID NO: 8 which variant retains the therapeutic, immunoprophylactic and diagnostic activities. The instant specification fails to demonstrate that a nucleic acid molecule encoding a polypeptide variant having at least 5%, 3% or 2% identity to SEQ ID NO: 8, if prepared by one of skill in the art, would retain all the functional or biological properties of the native HSP polypeptide of SEQ ID NO: 8. It should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. The precise structural composition of the recited polypeptide variant encoded by the claimed nucleic acid molecule is not disclosed, without which one of ordinary skill in the art cannot make and use the claimed product without undue experimentation. There is no evidence within the instant specification showing that the claimed polypeptide variant having an amino acid sequence which is at least 95%, 97% or 98% homologous to the amino acid sequence of the polypeptide of SEQ ID NO: 8, does in fact have the *S. pyogenes*-specificity as well as therapeutic and immunoprophylactic activity. There is no predictability that such a polypeptide variant having as much as 5%, 3% or 2% dissimilarity with the polypeptide of SEQ ID NO: 8, would remain therapeutically, immunoprophylactically and diagnostically functional. This is critical because the art reflects

sensitivity of proteins or polypeptides to alteration of even a single amino acid residue in its amino acid sequence. It is known in the art that an alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988), who showed that replacement of aspartic acid with alanine or asparagine at position 47 of the protein, transforming growth factor alpha, did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that a polypeptide molecule having as much as 2 to 5% dissimilarity with the native polypeptide of SEQ ID NO: 8 as recited, would have its primary, secondary or tertiary structure unchanged and would have the therapeutic and immunoprophylactic activities and *S. pyogenes*-specific diagnostic activity retained. The effects of such dissimilarity upon the polypeptide structure and function are unpredictable. Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein or polypeptide, with as much as 2-5% dissimilarity to the polypeptide of SEQ ID NO: 8, the therapeutic and immunoprophylactic activities and the *S. pyogenes*-specific diagnostic activity of the recited polypeptide variant encoded by the claimed nucleic acid molecule could not be predicted, based solely on the sequence identity,

nor would it be expected to be the same as that of the polypeptide of SEQ ID NO: 8. For example, if one nucleotide base in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 8 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 8. There is no certainty that amino acid substitutions at any position would yield a HSP polypeptide that retains the function and/or the specificity of the native HSP polypeptide of SEQ ID NO: 8. The specification fails to demonstrate that a polypeptide having 2-5% structural dissimilarity to SEQ ID NO: 8 would be functionally equivalent to the native polypeptide of SEQ ID NO: 8 particularly with regard to the therapeutic, immunoprophylactic and *S. pyogenes*-specific diagnostic activities. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore such modified molecules are not enabled as Applicants' invention. Applicants have not enabled the full scope of the invention as claimed for those nucleic acid molecules encoding polypeptide molecules, which are altered or varied. The enabling disclosure in the instant specification is limited to an isolated nucleic acid molecule encoding a polypeptide of SEQ ID NO: 8. Nucleic acid molecules encoding undisclosed and unidentified polypeptide molecules of at least 2 to 5% sequence non-identity encompassed in the claims are not enabled for their scope. Although a skilled artisan might envision making a number of changes in the reference polynucleotide sequence in accordance with Applicants' disclosure, it is highly uncertain that the encoded polypeptide variant as recited would be functionally equivalent to the native polypeptide of SEQ ID NO: 8. The altered polypeptide would vary in an unknown or unpredictable manner from the disclosed native polypeptide sequence. For these reasons, making and using of the instantly claimed nucleic acid molecule encoding a polypeptide variant having the intended function(s) or use is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the art, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first

paragraph.

Rejection(s) under 35 U.S.C § 102

18) Claim 2 is rejected under 35 U.S.C § 102(b) as being anticipated by Pohl *et al.* (GenEmbl accession number X89236, submitted 06/29/1995).

Pohl *et al.* taught an isolated *groEL* gene of the heat shock protein 60 (i.e., Hsp60) of *S. pyogenes*. See the attached sequence alignment report.

Claim 2 is anticipated by Pohl *et al.*

Rejection(s) under 35 U.S.C § 103

19) Claims 19-24 are rejected under 35 U.S.C § 103(a) as being unpatentable over Pohl *et al.* (GenEmbl accession number X89236, submitted 06/29/1995) in view of Sambrook *et al.* (*Molecular Cloning, A Laboratory Manual*, Second Edition, Cold Spring Harbor, pages 17.1-17.44, 1989) and Campbell AM (*In*: *Monoclonal Antibody Technology*. Elsevier Science Publishers, The Netherlands, Chapter 1, pages 1-32, 1984).

Pohl *et al.* taught an isolated *groEL* gene (i.e., *groEL* nucleic acid molecule) of the heat shock protein 60 or Hsp60 of *S. pyogenes*. See the attached sequence alignment reports. Pohl *et al.* do not teach an expression vector comprising the isolated *groEL* nucleic acid molecule comprising a constitutive or inducible promoter operatively linked to the nucleic acid molecule, with or without a selectable or identifiable marker, and a host cell such as a bacterial cell, yeast cell or insect cell comprising the vector.

However, expression of an art-known isolated nucleic acid molecule using recombinant techniques via an expression vector comprising an inducible promoter operatively linked to the nucleic acid molecule with a selectable or identifiable marker, and expression of such a vector via a bacterial cell such as *E. coli,* was well known and routinely practiced in the art at the time of the invention. For instance, Sambrook *et al.* taught how to recombinantly express a protein from a cloned gene using an expression vector as recited. Sambrook *et al.* taught that given a known DNA sequence encoding a protein of interest, large amounts of the protein fused, for example with beta-galactosidase, can be made in *E. coli* using standard art known techniques and that such proteins are useful for generating antibodies (see page 17.29, first, second and third full paragraphs; and pages 17.3-17.9.1).

Campbell taught that it is customary now for any group working on a macromolecule to both clone the genes coding for the macromolecule and make antibodies to it sometimes without a clear objective for their application. Campbell also taught that chromosomal protein macromolecules can be studied in the field of research using these antibodies (see page 29, last paragraph). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to clone or express Pohl's isolated *S. pyogenes* Hsp60 gene using art known recombinant techniques taught by Sambrook *et al.* to produce the vector and the host cell of the instant invention, with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing an antibody to the expressed *S. pyogenes* Hsp60 protein macromolecule in order to study the protein for research purposes as taught by Campbell.

Claims 19-24 are *prima facie* obvious over the prior art of record.

20) Claim 31 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Pohl *et al.* (GenEmbl accession number X89236, submitted 06/29/1995) as applied to claim 2 above.

The teachings of Pohl *et al.* are explained above, which do not disclose a composition comprising the gene in the presence of a pharmaceutically acceptable carrier.

However, adding a pharmaceutically acceptable carrier to an isolated gene already disclosed in the prior art is routine and very conventionally practiced in the art especially when studying its physicochemical or biological properties. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add an art-known pharmaceutical carrier to the prior art gene to produce the instant invention with a reasonable expectation of success, since it is quite conventional to have an isolated gene mixed with in a pharmaceutical carrier in order study its physicochemical or biological properties.

Claim 31 is *prima facie* obvious over the prior art of record.

Remarks

21) Claims 2, 6, 19-24, 31, 38, 39 and 41-45 stand rejected.

Claims 3, 5, 7, 33, 35 and 40 are objected for including non-elected subject matter.

22) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions

24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

23) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

24) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, M.S., Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

April, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER

LYNETTE R. F. SMITH
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